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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/576,858	Applicant(s) SNYDER ET AL
	Examiner Scott Priebe	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002 and 20 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,54 and 71-91* is/are pending in the application.

4a) Of the above claim(s) *48 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s): *20*
4) ☐ Interview Summary (PTO-413) Paper No(s).
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Continued Prosecution Application

The request filed on 4/29/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/576,858 is acceptable and a CPA has been established. The amendments filed 2/28/02, 4/29/02 and 6/20/02 have been entered. An action on the CPA follows.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

Claims 48 and 54 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claim Rejections - 35 USC § 112

Claims 71-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claims 71-75, 76-79 are directed to a method for expressing a therapeutic protein in the liver of a mammal, and broadly recites administering a rAAV to "a mammalian cell." This broadening of the invention to include mammalian cells other than mammalian *liver* cells is not supported by the specification as originally filed. The original specification explicitly states that cells of a mammalian liver, either *in vivo* or *ex vivo* are the intended target cells (e.g. Summary of Invention, pages 10-11; page 22, lines 8-9).

Claims 80-85 are directed to a method of treating a liver disease or disorder and claims 86-91 are directed to a pharmaceutical composition for treating a liver disorder. The therapeutic proteins are factor VIII, factor IX and GM-CSF. The specification describes using factor VIII and factor IX to treat blood diseases (page 19, lines 11-16), not a liver disease or disorder as claimed. The specification (page 21, lines 31-35) describes an embodiment where GM-CSF is the protein that "may be useful for gene therapy", but does not describe what disease or disorder it would be useful for treating. The specification describes liver-specific diseases (page 19, lines 27-31) and the protein to be encoded for each. It does not teach using sequences encoding factor VIII, factor IX or GM-CSF for a liver disease.

Claims 71-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. .

The claims are broadly drawn to methods of expressing a therapeutic protein encoded on a rAAV in the liver of a mammal (claims 71-79), methods of treating an liver disease by gene therapy (claim 27), methods of treating an unspecified disease not limited to liver disease by gene therapy where the rAAV encodes factor VIII, factor IX, or GM-CSF (claims 80-85), and pharmaceutical compositions for treating liver disease (claims 86-91). The claimed methods (and use of the claimed products) involve administration of a recombinant adeno-associated virus, rAAV, to liver cells either *in vivo* or of liver cells *ex vivo* followed by introduction of the transduced liver cells into the liver. Although the method of claims 71-79 is not limited to treatment of disease, the specification describes no other use for the claimed method, and there is no evidence of record identifying another well-established use for the general method. Therefore, in light of the specification claims 71-79 are interpreted as being implicitly directed to gene therapy, and are so evaluated for compliance of the specification with the enablement requirement. The implied use of this method to evaluate AAV as a suitable gene therapeutic vector does not meet the utility requirement, and hence the enablement requirement for how-to-use, since such use would constitute using the invention for research on itself.

The specification provides general guidance limited largely to the listing of many diseases that may be treated, therapeutic transgenes, promoters to be used to express the transgene with little guidance as to which promoters would be useful for which applications, a few methods of administration, and the teaching (see page 31, from line 15) regarding dosage and regimen of treatment that the skilled artisan should determine this by trial and error experimentation. While

most of the claims are limited to liver-specific promoters or enhancers, the specification does not teach that such promoters are preferable to promoters which are not tissue specific. The specification provides working examples only for transfer of rAAV that subsequently expresses human clotting factor IX to the liver of a healthy mouse *in vivo*. In addition, the promoter used is a constitutive retroviral viral promoter, not a liver-specific promoter. No working examples readable on the claims or of gene therapy are provided, nor are suitable model systems described except for the use of hemophilic dogs for treatment with rAAV expressing factor IX. At page 10, lines 1-10 of the specification, it is stated that in such dogs retroviral vector-mediated gene therapy resulted in persistent, but subtherapeutic expression of factor IX, while adenoviral-mediated gene therapy resulted in brief therapeutic expression, but that immunotoxicity of the vector results interfering with extended expression. These problems are cited as the impetus to develop AAV vectors for transduction of liver cells for gene therapy. There is no evidence presented in the specification that using AAV vectors would succeed, where retroviral and adenoviral vectors had failed. The working examples do not use an accepted model for treatment of hemophilia, or compare the use of an AAV vector to using a retroviral vector or adenoviral vector.

Gene therapy is a highly unpredictable and undeveloped art. Orkin et al. reviews the infant state of the art of gene therapy to just before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained

in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The instant application provides no guidance beyond the prior art, and offers no solutions to these problems raised by Orkin et al. Ross et al. (Hum. Gene Ther. 7: 1781-1790, 1996) indicates in a follow-up of the Orkin report, that the situation had not changed up till the time the instant invention was made.

Orkin et al. provides little discussion on using AAV for gene therapy other than to say that little experience has been obtained due to the inability to produce large amounts of rAAV, which raises an issue of the suitability of AAV for gene therapy at the time the invention was made. The difficulty in preparing large amounts of rAAV for treatment is exacerbated by the low transduction efficiency. As taught by Russell et al. (Proc. Natl. Acad. Sci. USA 91: 8915-8919, 1994) it requires thousands of vector particles to transduce a single dividing cell *in vitro*, lacking immune mediators, mucous secretions, digestive enzymes and other potential inhibitors of transduction likely to be encountered *in vivo*. Consequently, it is unclear how effective rAAV would be in gene therapy (see Russell et al., page 8919, para. 1). With respect to rAAV vectors

for use in gene therapy, the lack of experience in their use is an additional source of unpredictability.

Fisher et al. (J. Virol. 70(1): 520-532, 1996) describes experiments on using rAAV vectors to transduce liver cells *in vitro* and *in vivo.* The reference concludes that the low efficiency of rAAV transduction limits its usefulness as a gene therapy vector unless further advances are made because of the step of converting a single-strand rAAV to double-strand, which requires helper virus functions. In addition, expression of the transgene form a rAAV is influenced by factors other than the amount of double-strand rAAV, possibly requiring helper virus functions for efficient transport to and accumulation in the cytoplasm of transgene mRNA The reference also discloses the difficulty in producing suitable quantities of purified rAAV particles. (See Fisher et al., Abstract, page 520 for overview; para. bridging pages 520-521; page 527, col. 1, para. 1; page 529, col. 1 through pages 531 and 532). Chen et al. (Hum. Gen. Ther. 8: 125-135, 1997) discloses that the efficiency of AAV vectors for transduction and expression of clotting factor IX in cultured cells was lower than for retroviral vectors both in terms of transduction and expression (see Abstract, page 125, for overview). A similar result was obtained by Koeberl et al. (Am. J. Hum. Genet. 57, suppl. 4: A43, 1995). Koeberl et al. (Proc. Natl. Acad. Sci. USA 94: 1426-1431, 1997) carried out experiments similar to, with nearly the same rAAV vector, those disclosed in the working examples, and achieved sustained levels of factor IX expression comparable to those reported in the instant specification. The level of transduction was comparable to that using retroviral vectors, and required co-administration of wild type AAV

and γ-irradiation to achieve. The reference teaches that plasma levels of 1-2 ng/ml FIX were far below therapeutic levels for humans of 100 ng/ml. As noted above, the specification teaches that retroviral delivery of a factor IX expression construct to hemophiliac dogs resulted in subtherapeutic expression. As shown by the art cited, rAAV delivery is not expected to be any better than therapeutically unsuccessful retroviral delivery without some further advance requiring inventive experimentation and development to improve rAAV transduction efficiency and transgene expression. Obtaining transgene expression from a rAAV delivered to the liver is not new. However, obtaining therapeutically relevant transgene expression would be. Those of skill in this art, before and after the instant invention was made, recognized that rAAV transduction efficiency and transgene expression were insufficient to achieve therapeutic goals. The instant specification does not provide solutions to these problems.

Claims 74, and 80-91 are directed to embodiments wherein the therapeutic protein is factor VIII of GM-CSF. There is no guidance in the specification as to how to make a rAAV comprising a sequence encoding factor VIII. The coding sequence for factor VIII alone is over 7 kb, addition of transcriptional control elements would increase that size. Such an insert is too large for an AAV vector to be packaged into virions (Chao et al., Blood 95(5): 1594-1599, 2000, see p. 1594, col. 2; Chuah et al., J. Gene Med. 9: 3-20, 2001). It is well-known in the art (Ross et al., Table 2) that the maximum insert size for a gutless AAV vector is about 5 kb, not 10kb as indicated in the specification. The specification does not enable how to make the rAAV required for the factor VIII embodiment. The specification (page 21, lines 31-35) describes an

embodiment where GM-CSF is the protein that "may be useful for gene therapy", but does not describe what disease or disorder, much less a "liver-specific disease or disorder" it would be useful for treating, i.e. there is no assertion of a substantial utility for this embodiment. The specification contains no guidance on how to use the GM-CSF embodiment, e.g. what patients to administer it to, and therefore does not enable how to use it.

In view of the unpredictable and undeveloped state of gene therapy as shown by the prior art, the minimal guidance in the specification on rAAV-mediated gene therapy in general and the lack of guidance specific for the treatment of specific diseases, the lack of relevant working examples, the high unpredictability of gene therapy in the art, and the inventive experimentation that would be required to overcome the problems known in the art, it would require undue experimentation in order to practice the invention claimed.

Applicant's arguments filed 2/28/02 have been fully considered but they are not persuasive. Applicant has provided several references published well after the instant invention was made that allegedly show that the claimed invention was successful. However, applicant has not indicated how the specification would have guided one of skill in the art to practice these later methods. Wang et al. discloses that several attempts by others to achieve therapeutically relevant levels of cFIX expression failed (page 154, col. 2). The results of these attempts, including by Applicant, were published well after the instant invention was made. Wang et al. attributed their success to the specific synthetic promoter they developed in conjunction with a

specific and enhancer element (page 158, col. 2). The instant specification does not teach either the promoter or the enhancer.

Chuah et al. disclosed that for factor VIII gene therapy with rAAV, a major challenge that had to be solved was to design a factor VIII expression cassette that was small enough to be accommodated by AAV (page 11, col. 1-2). The specification provides no guidance in this regard. When a single vector expressing a B-domain deleted factor VIII was used, a significant anti-FVIII response was observed, and it is unclear if the expression level was therapeutically relevant. Chao et al. is directed to solving the challenge of how to make a rAAV that expresses FVIII using modifications not taught in the instant specification. The second example involved expressing the heavy and light chains of mature FVIII on separate AAV vectors, which is not taught in the specification. For factor IX, one example used the promoter disclosed by Wang et al., not taught in the specification. The other examples utilized ubiquitous mammalian or viral promoters, not liver-specific promoters. One such ubiquitous promoter used was the CMV promoter, however, in this example therapeutically relevant expression was not achieved.

Koeberl et al. (2000) is directed to systemic delivery to liver where the protein is G-CSF for increasing neutrophil populations in the treatment of neutropenia. However, the specification does not teach this use, or any other use for expressing G-CSF from the liver.

Kay et al. discloses delivery of rAAV to muscle, not liver, and did not involve liver-specific promoters. Liu et al. is not directed to delivery of rAAV to a mammal, much less the

liver. It is directed to a method of making mature dendritic cells in culture. The relevance of Kay et al. and Liu et al. to the rejection is unclear.

Claims 71-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71-85 are incomplete. Claims 71-79 is directed to a method for expressing a therapeutic protein in the liver. However, the method steps recited only require mammalian cells to be infected, without indicating where the cells are when transfected, e.g. in the liver, in the brain, on a lab bench, etc., or after they are transfected. Claim 73, for example does not require the infected cells to be administered to the liver, they could be fed to the mammal. Consequently, there is no nexus between infecting cells, and expression in the liver as stated in the preamble. Claim 71 should be amended to indicate that liver cells are either transfected *in vivo*, or transfected *ex vivo* and introduced into the liver. Claims 80-85 recite administering the rAAV to liver cells, but again does not require that the liver cells be in the mammal, as would be indicated by the preamble. For example, the claim reads on transfecting a liver cell from the mammal *ex vivo*, but does not require placing the cell back into the liver.

Claim Rejections - 35 USC § 102 & 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 71-91 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Srivatava et al. (US 2001/0051611 A1).

See entire document, e.g. Abstract, paragraphs 0008, 0009, 0013, 0015, 0016, 0023, 0025, 0033-0035, 0048-0051, claims 1-11.

Claims 86-88, and 91 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Samulski et al. (US 6,268,213 B1). Claims 86 and 89 are rejected under 35 U.S.C. 103(a) as

being unpatentable over Samulski et al. (US 6,268,213 B1) in view of applicant's admission of prior art (page 25, line 25 to page 26, line 2).

See col. 14, disclosing a rAAV composition for the treatment of hemophilia B, where the rAAV comprises coding sequence for factor IX operably linked to any liver specific promoter. Samulski et al. does not disclose specific liver-specific promoters, however, since Samulski et al. teaches that any such promoter can be used, one of skill in the art would select from those known in the art which the instant specification identifies.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER